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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,899	12/06/2005	Herwig Gaston Emiel Van Marck	VIP-0022-USPCT	2752

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EXAMINER	
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ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,899	VAN MARCK ET AL.	
	Examiner	Art Unit	
	Karlheinz R. Skowronek	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-11 and 13-16 are pending.

Claim 12 is cancelled.

Claims 1-11 and 13-16 are being examined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 06 December 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Drawings

The drawings are objected to because the text in figure 17 is too small to reproduce clearly. As indicated in 37 CFR 1.84(p), letters must measure at least 1/8 inch in height. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the

drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities:

> The disclosure is objected to because it contains an embedded hyperlink and/or other forms of browser-executable code (see specification p. 6, line 18-19). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

The abstract of the disclosure is objected to because the last sentence of the abstract does not end with a period. Correction is required. See MPEP § 608.01(b). It is noted that three copies of the abstract exist in the record. Two of the three copies are the first page of the application's WIPO publication. The third copy is a page from the specification, p. 54, and the last sentence of which does not end in a period.

Claim Objections

Claims 3, 4, 6, and 11 objected to because of the following informalities:

Claim 3, at line 3, the article "an" is missing from the phrase "calculate average".

Claim 4, at line 10, the article "a" is missing from the phrase "calculate correlation".

Claim 4 seems to be missing a "for" preceding the phrase "all previous iterations" in lines 8 and 15.

Claim 4, lines 8 and 15 have an unmatched parenthesis.

Claim 6 contains multiple periods at lines 14, 22, and 26.

Claim 6 contains bullet points to indicate sub-steps. It is suggested that letters, numbers or roman numerals be used.

Claim 6 is missing "the" in lines 9, 11, 14, 17, 19, 22, and 26.

Claim 11 contains a typographical error, "to obtaining a", at line 3.

Appropriate correction is required.

Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 is directed to a method of identifying a mutation using the method of claim 1. This objection can be overcome by cancelling claim 7.

Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 depends from

claim 8, directed to a method which has incorporated the method of claim 1. Claim 9 depends from claim 8. Since claim 8 has incorporated the method of claim 1, claim 9 does not further limit claim 8.

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Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 16 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 16 is directed to a computer program product comprising a computer readable storage medium and a computer program mechanism. The specification doe not provide a definition for a "computer program mechanism". The term is being interpreted as broadly as reasonable to encompass both computer-executable forms of programs and as program code or listing. As a program code or listing it is descriptive material per se and as such is non-statutory.

Claim 16 is also non-statutory with respect to the computer readable medium. The specification does not indicate the types of medium that are envisioned. Giving the computer readable medium its broadest reasonable interpretation, the medium reads on both media such as optical discs and as media such as carrier signals. Carrier signals are a natural phenomenon and are non-statutory. Thus the claim is directed to non-statutory subject matter.

Claim 13 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 13 is directed to the use of the method

of claim 1. Claim 13 is not statutory because it is not a proper process claim as it does not recite active process steps.

Claims 1-11 and 13-16 are drawn to a process, apparatus that performs the process and a computer program. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

> The question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to -- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See *In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to

be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-11 and 13-16 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. The process, apparatus and program are directed to the quantification of at least a mutation to a drug resistance phenotype of HIV by performing a linear regression on matched genotype-phenotype data. The process or apparatus do not return a tangible result to the practitioner of the process or apparatus. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the experimentally determined measurements" in line 22. There is insufficient antecedent basis for this limitation in the claim. Claims 2-11 and 13-16 are also rejected because they depend from claim 1, and thus contain the above issues due to said dependence.

Claim 4 recites the limitation "the residue" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites the limitation "the phenotypic measured value" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites the limitation "the global average" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation "said computer program" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Regarding claim 6, the phrase "for example" or "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 13 is indefinite because the claim recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 6 is unclear with respect to the recitation of the phrases "as value" and "remove value from" in lines 9, 14, 17 and 21. Several different values are presented in the claim and the use of the phrases in the context of the claim suggest that the term "value" is not the same at each occurrence of either phrase. Thus it is unclear which value is being referred to in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7-11, 13-15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Servais et al. (Antiviral Therapy, Vol. 6, p. 239-248, 2002), in view of Carter et al. (US PG PUB 2004/0138826).

The claims are drawn to a method, system and program for quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold resistance where the log fold resistance can be expressed as the sum of the mutation contributions. In some embodiments, the method further comprises obtaining a genetic sequence of an HIV strain and identifying a pattern of mutations that are associated with resistance. In some embodiments, correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set. In some embodiments, the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance.

Servais et al. shows a method of quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold resistance. Servais et al. shows that a linear mixed effects regression analysis was performed to measure the association between the quantitative predictor variable (the mutations) and the longitudinal data (the resistance phenotype) (p. 241, col. 2). Servais et al. further shows that through the use multiple regressions of the genotype-phenotype data, the additive nature of individual mutation is identified (p. 242, col. 1-col. 2). In figure 2, Servais et al. shows results of the correlation between mutational patterns of HIV protease inhibitors and log fold

resistance. Servais et al. shows an embodiment in which the genetic sequence of an HIV strain is obtained via sequencing (p. 240, col. 2). Servais et al. shows an embodiment in which a pattern of mutations is identified that is correlated with a resistance phenotype (p. 240, col. 1-2). Servais et al. shows an embodiment in which the resistance of HIV strains is tested in a patient and is used to select the drug with the lowest predicted fold resistance (p. 246, col. 1).

Servais et al. does not show the equation: $pFR = \beta_A M_A + \beta_B M_B + \beta_n M_n + \varepsilon$.

Carter et al. shows a method of statistical analysis of interactions among mixtures of agents. Carter et al. shows that interaction between agents to produce a particular response can be modeled statistically with the additivity equation $\mu = \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_{12} + \beta_0$ [0014-0021]. Carter et al. shows the equation can be used to determine the contributions of the agents in a mixture of agents as synergistic, antagonistic or no interaction [0027]. Carter et al. shows that agents can be something other than a chemical substance [0093]. Carter et al. suggest that agents can be a condition, characteristic, or phenomena that an individual is exposed to. Mutations fit the criterion of a characteristic insofar as mutations are characteristics that define the activity a given protein, thus the term agent reads on the term mutation. Carter et al. describes that the methods and equation are not limited to two components. Carter et al. shows the general form of the equation suitable to any number of components or agents [0109]. Carter et al. shows the β variable represents synergism or antagonism [0024]. The variable x in the equation of [0014] is the concentration of agent in the mixture an represents the degree to which the agent is present in the mixture [0013].

Carter et al. shows this more clearly by normalizing the sum of the degree of an agent's presence to 1 [0111]. The β_0 term of the equation is an unknown intercept which Carter et al. shows represents the difference between the model and the experimentally determined data [0096]. Carter et al. shows that the additivity equation is equivalent to a simple linear regression [0679]. Carter et al. shows an embodiment in which correlations are removed from the dataset using an algorithm that tracks the predicted response as mutations are removed from the data set [0040-43]. Carter et al. shows an embodiment in which the method is applied iteratively in cases where small data sets are used [0101].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear regression analysis of genotype-phenotype HIV strain drug resistance data with the statistical regression analysis of mixtures of agents because the substitution of the different regression analysis methods for one another would have yielded predictable results.

Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Servais et al. in view of Carter et al. as applied to claims 1, 2, 7-9, 11, 13-15, and 16 above, and further in view of Hughes et al. (Biometrics Vol. 55, No. 2, p. 625-629, June 1999).

The claims are drawn to a method, system and program for quantifying the contributions of mutations to drug resistance of an HIV strain by performing a linear regression analysis on matching genotype-phenotype data to generate a log fold

resistance where the log fold resistance can be expressed as the sum of the mutation contributions. In an embodiment, censored values are replaced by maximum-likelihood estimation.

Servais et al. in view of Carter et al. as applied to claims 1, 2, 7-9, 11, 13-15, and 16 above shows a method of quantifying the contributions of mutations to drug resistance of an HIV strain.

Servais et al. in view of Carter et al. as applied to claims 1, 2, 7-9, 11, 13-15, and 16 above do not show an embodiment in which censored values in the are replaced by a maximum likelihood estimation.

Hughes et al. shows an embodiment in which censored values are replaced by maximum likelihood estimation (p. 625, col. 1). Hughes et al. suggests that the advantage of estimating and replacing censored data is that significant bias is avoided in the analysis of mixed effects and variance (p. 625, col. 1).

It would have been obvious to one of skill in the art at the time of invention to modify the method of quantifying the contributions of mutations to drug resistance of an HIV strain of Servais et al. in view of Carter et al. as applied to claims 1, 2, 7-9, 11, 13-15, and 16 above with the maximum-likelihood estimation of censored data of Hughes et al. because Hughes et al. shows significant bias is avoided in the analysis of mixed effects and variance when censored data is estimated which is a desirable effect.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is (571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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